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Knee osteoarthritis and all-cause mortality: the Wuchuan Osteoarthritis Study

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SUMMARY

Background: Previous studies showed that knee osteoarthritis (OA) is associated with increased mortality in Caucasians. While prevalence of knee OA is higher in Chinese than in Caucasians, no study has examined whether knee OA increases mortality in Chinese population.
Methods: Between 8/2005–10/2005 1025 residents aged ≥50 years were recruited in randomly selected rural communities in Wuchuan, China. Subjects completed a home interview and had weight-bearing posteroanterior semiflexed view of radiographs at tibiofemoral joints and skyline view of radiographs at patellofemoral joints, and were followed until end of 2013. A knee was defined as having radiographic osteoarthritis (ROA) if either Kellgren/Lawrence (KL) score at tibiofemoral joint ≥2 or presence of OA at patellofemoral joint based on OARSI criteria. Symptomatic knee osteoarthritis (SxOA) was defined if both pain (i.e., knee pain occurred on most days in past month) and ROA were present at the same knee. We examined the relation of knee SxOA and knee ROA to the all-cause mortality, respectively, using Cox-proportional hazard models adjusting for potential confounders.
Results: Over the follow-up period 99 subjects died. The mortality rates were 32.6 (95% confidence interval (CI): 19.6–54.0) and 10.9 (95% CI: 8.8–13.5) per 1000 person-years among subjects with and without SxOA, respectively. Multivariable adjusted hazard ratio of all-cause mortality for knee SxOA was 1.9 (95% CI: 1.0–3.5). However, no such association was observed for knee ROA (hazard ratio = 1.2, 95% CI: 0.7–1.9).
Conclusions: Knee SxOA was associated with an increased risk of all-cause mortality among the residents in the rural areas of China.

Introduction

Knee osteoarthritis (OA) is a common joint disorder and a leading cause of disability among the elderly[1–3]. Recently, a population-based cohort study conducted in England reported that all-cause mortality among patients with knee or hip OA was 55% higher than that among the general population[4]. Results from the Ontario Hip and Knee Study also indicated that the severity of knee and/or hip OA was strongly associated with higher all-cause mortality.[5]

Knee OA is more common among Chinese than among Caucasians[6,7]. For example, prevalence of symptomatic knee osteoarthritis (SxOA) was 40% higher in women in Beijing than their counterparts in Framingham, US[6]. Interestingly, in a population-based cohort study conducted among residents living in rural areas in Wuchuan, China, while the overall prevalence of radiographic knee OA among rural residents was similar to that among urban residents in Beijing, China, the SxOA was twice as prevalent in Wuchuan as that in Beijing.[7]

Approximately half of the population in China lives in rural areas, and socioeconomic status and health care system in rural areas are not as well developed as in urban areas. If knee OA is indeed associated with an increased all-cause mortality as was

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observed in Caucasian population, we would expect that such an association would exist among residents in rural areas of China. The aim of this study was to evaluate the association between knee OA and all-cause mortality among participants in Wuchuan Osteoarthritis Study, a longitudinal study conducted in rural areas of China.

Participants and methods

Study design and participants

Wuchuan Osteoarthritis Study is a longitudinal study of risk factors for knee OA. The details of Wuchuan Osteoarthritis Study have been published previously[7]. Briefly, 1025 residents aged ≥50 years were recruited using door-to-door enumeration in randomly selected rural communities in Wuchuan, China from August 2005 to October 2005. Subjects completed a home interview and had a hospital examination including weight-bearing posteroanterior semiflexed view of radiographs at tibiofemoral joints and skyline view of radiographs at patellofemoral joints. A follow-up visit of study participants was conducted approximately 8 years later. During the follow-up visit the participants were queried with the same questionnaires and received the same clinical examinations as that in the baseline visit.

Assessment of knee OA at baseline

Weight-bearing posteroanterior semiflexed view of radiographs at tibiofemoral joints and skyline view of radiographs at patellofemoral joints were obtained in baseline visit. The detailed description of knee radiograph reading has been published previously[7]. In brief, an investigator from Wuchuan Osteoarthritis Study was trained at Boston University. Preliminary reading of batches of randomly selected films continued until the reader reached a high level of inter-rater agreement using the readings from the primary reader of the Beijing Osteoarthritis Study as a gold standard. For each batch (approximately 50 radiographs), four previously read knee radiographs from the Wuchuan Osteoarthritis Study were fed back to the reader to test intra-rater reliability. Each knee was evaluated for the presence of osteophytes, joint space narrowing (JSN), sclerosis, and cysts on a 0–3 scale, and radiographic osteoarthritis (ROA) at tibiofemoral joint was graded using the Kellgren/Lawrence (KL) scale (graded 0–4, where 0 = none; 1 = possible osteophytes only; 2 = definite osteophytes and possible JSN; 3 = moderate osteophytes and/or definite JSN; and 4 = large osteophytes, severe JSN, and/or bony sclerosis). A knee was defined as having tibiofemoral ROA if its KL score was ≥2. ROA at patellofemoral joint was identified if there is an osteophyte of severity grade ≥ 2 or if there is moderate to severe JSN (>=2 on a 0–3 scale) with concurrent grade 1 osteophyte in the patellofemoral joint. The weighted kappa on KL grade for inter-rater reliability was 0.80 (95% confidence interval (95% CI): 0.72–0.88) and the intra-rater reliability was 0.92 (95% CI: 0.86–0.99)[7]. Knee pain symptoms were asked for each participant using the following questions “Did knee pain occur on most days in the past month?” We defined a knee as having ROA if either K/L score at TF joint ≥2 or presence of patellofemoral ROA. SxOA was recorded if both pain and ROA were present at the same knee. Physical examination of the knees was not incorporated into the classification of either ROA or SxOA.

Assessment of mortality

Information on death that occurred during the follow-up visit was obtained either by interviewing relatives of the deceased subject or by searching documents from the Birth and Death Registry of the local community office.

Assessment of covariates

Information on age, sex, education level, income, level of occupational physical activity and comorbidities (e.g., hypertension, diabetes, heart diseases, chronic lung diseases, renal disorders and malignant tumor) was collected at baseline using a standard questionnaire. Height was measured twice for each subject, using a wall-mounted stadiometer and weight was assessed using a balance beam scale with a precision to 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Subjects' occupational physical activity was assessed based on the longest job they took during their lifetime. Levels of occupational physical activity were grouped into four categories: sedentary, light physical activity, moderate physical activity and heavy physical activity. The majority of the participants were engaged in heavy agriculture manual work. We used a specific question to assess an individual comorbidity. For example, “Did you have hypertension?” Similar questions regarding diabetes, heart diseases, chronic lung diseases, renal disorders and malignant tumor were also queried, respectively.

Statistical analysis

Using a *t*-test for continuous variables and a chi-square test for categorical variables, we compared the characteristics of the participants according to presence or absence of knee OA. Person-years of follow-up for each subject were computed as the amount of time from the date the radiographs was obtained to the date of the first of the following events: death; the last date of contact for those lost to follow-up; or follow-up visit in 2013. All-cause mortality for SxOA was calculated by dividing the number of death by the number of person-years of follow-up. We plotted Kaplan–Meier survival curves to determine the cumulative rate for all-cause mortality according to the status of SxOA. We fitted a Cox proportional hazards model, using age as the time scale, to examine the relation of SxOA to the risk of all-cause mortality. Since age instead of follow-up time was used as the time-scale in the regression model the hazard function can be directly interpreted as the age-specific mortality function[8]. In the multivariable regression model we adjusted for baseline age, sex, BMI, education level, income, levels of occupational physical activity and comorbidities, including hypertension, diabetes, heart diseases, chronic lung diseases, renal disorders and malignant tumor. All comorbidities, each of them coded as a dichotomous variable, were entered in the multivariable adjusted Cox-proportional regression model. We took the same approach to examine the relation of radiographic knee OA and all-cause mortality.

Results

Of 1025 participants in the Wuchuan Osteoarthritis Study, 63 (6.1%) had SxOA and 181 (17.7%) had radiographic knee OA at baseline. Baseline characteristics of subjects are shown in Table I. Women, old age, low annual income, high BMI were more likely to have SxOA than their counterparts. Levels of education and occupational physical activity were not strongly associated with the prevalence of SxOA. Similar findings were observed when the distribution of baseline characteristics was compared between subjects with and those without radiographic knee OA.

During the 8-year follow-up period, 99 participants died. All deaths were confirmed by documents at the Birth and Death Registry of the local community office. Of them, 15 occurred among subjects with SxOA and 84 among those without the disease. The corresponding number of death was 28 and 71, respectively, among subjects with and without radiographic knee OA. Among 1025

Table I
Baseline characteristics of participants in Wuchuan Osteoarthritis Study

Characteristics	Symptomatic knee OA		Radiographic knee OA	
	No ($n = 962$)	Yes ($n = 63$)	No ($n = 844$)	Yes ($n = 181$)
Female (%)	49.4	71.4	47.6	65.2
Age (years, mean ± SD)	56.0 ± 7.8	62.2 ± 8.6	55.3 ± 7.3	61.6 ± 9.2
Education (%)				
Elementary school	69.1	66.7	69.6	66.3
Middle school	25.5	30.2	25.2	28.2
High school and more	5.4	3.2	5.2	5.5
Annual income > 3000 yuan	55.8	39.7	61.3	40.9
BMI (kg/m^2, mean ± SD)	22.3 ± 3.2	23.9 ± 3.7	22.2 ± 3.1	23.6 ± 3.8
Levels of physical activity (%)				
Light	0.7	0.0	0.6	1.1
Moderate	7.7	15.9	7.0	13.8
Heavy	91.6	84.1	92.4	85.1

participants recruited at baseline, 11 (1.1%) subjects' vital status cannot be confirmed due to lost to follow-up.

As shown in Fig. 1, all-cause mortality was higher among subjects with SxOA (32.6/per 1000 person-years, 95% CI: 19.6–54.0) than that among subjects without the disease (10.9/1000 person-years, 95% CI: 8.8–13.5). After adjustment for baseline age, sex and other confounders, subjects with SxOA had 90% higher mortality rate than those without the disease (hazard ratio = 1.9, 95% CI: 1.0–3.5) (Table II). All-cause mortality was also higher among subjects with radiographic knee OA (20.1/1000 person years, 95% CI: 13.9–29.1) than those without it (10.5/1000 person-years, 95% CI: 8.3–13.3) (Fig. 1); however, after adjusting for potential confounders, the association was not statistically significant (hazard ratio = 1.2, 95% CI: 0.7–1.9) (Table II). When we excluded 11 subjects whose vital status can't be confirmed, the effect of SxOA on all-cause mortality did not change materially (hazard ratio = 1.9, 95% CI: 1.0–3.4).

Discussion

In this population-based prospective cohort study conducted among rural areas in China, we found that subjects with SxOA had an increased risk of all-cause mortality; however, no such an effect was observed for those with radiographic knee OA. The magnitude of association between SxOA and all-cause mortality is even greater among rural residents in China (hazard ratio = 1.9, 95% CI: 1.0–3.5) than that reported in England (standardized mortality ratio = 1.55, 95% CI: 1.41–1.70).[4]

Knee OA is the most common joint disorder among the elderly, constituting a tremendous disease burden due to pain, functional limitation and physical disability. Recently a few studies have reported that knee OA may also be associated with excess mortality[4,5]. While the underlying biologic mechanisms linking knee OA to mortality are not fully understood, several explanations have been proposed to account for such an association. First, subjects with SxOA are likely to suffer from physical disability[9]. Lack of physical activity[10], especially walking disability[11], is one of the well-established risk factors for death from cardiovascular diseases[12]. Second, subjects with SxOA are also likely to take various medications, including non-steroidal anti-inflammatory drugs (NSAIDs), to relieve their joint symptoms, and studies have found that NSAIDs use was associated with an excess mortality from gastrointestinal and cardiovascular diseases.[13]

Several characteristics of our study are noteworthy. First, the data are from population-based cohorts of residents living in rural areas of China, and participants were followed over a long period of time, permitting an assessment of knee OA on the mortality that may require many years to appear. Second, we used the standard definition to define radiographic and SxOA and reliability of assessing the presence of disease is high; thus misclassification of the exposure is unlikely to account for the current findings. Third, the rate of lost to follow-up is low and we were able to collect information on death through either an interview with the relatives of deceased subjects or via documents from a government agency. Finally, most covariates, such as male gender, underweight, and comorbidities were associated with an increased risk of all-cause mortality, whereas high income and high levels of education were associated with a low risk of all-cause mortality (Appendix) although the effects estimates of some covariates were not statistically significant owing to small sample size. Our study has some limitations as well. First, the number of subjects was relatively small; nevertheless, we were still able to find an increased risk of all-cause mortality from SxOA. Second, subjects with knee OA in our study are the prevalent cases; thus the effect of SxOA on mortality is likely to be underestimated owing to potential prevalent exposure bias in which relatively larger proportion of subjects who were most susceptible to death died before the study enrollment among those with knee SxOA than those without it[14]. Third, smoking was not assessed in the current study and we were unable to control for its potential confounding effect on the association between knee OA and all-cause mortality. Finally, we did not collect data on specific cause of death; thus we cannot assess whether SxOA is associated with cause-specific death.

In conclusion, this prospective, population-based study among residents in rural areas of China shows that symptomatic, but not

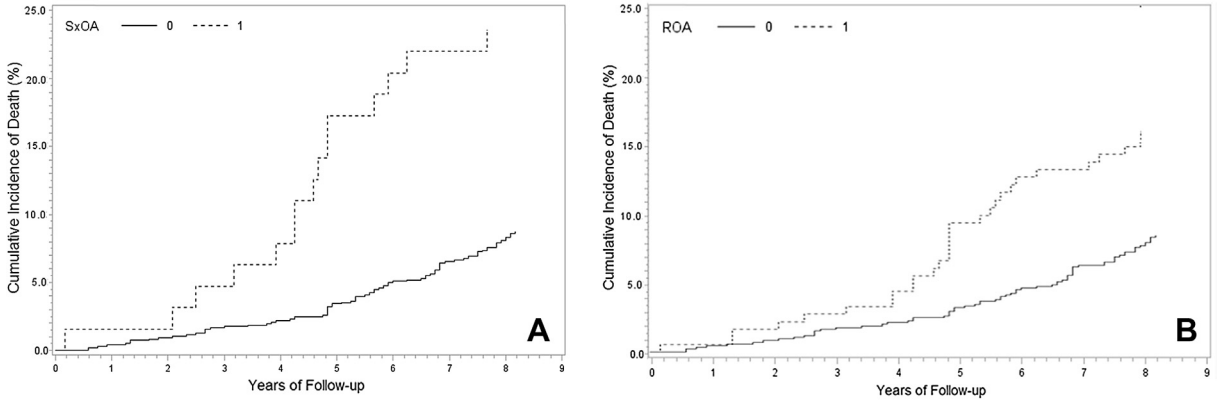

Fig. 1. All-cause mortality according to the (A) SxOA and (B) Radiographic knee OA in Wuchuan Osteoarthritis Study.

Table II
Association between knee OA and all-cause mortality among participants, in Wuchuan Osteoarthritis Study

Knee OA status	Number of subjects	Follow-up years	Number of death	Mortality rate (1/1000 P-YRs, 95% CI)	Multivariable-adjusted hazard ratio (95% CI)*
Presence of SxOA					
No	962	7691.3	84	10.9 (8.8, 13.5)	1.0 (reference)
Yes	63	460.8	15	32.6 (19.6, 54.0)	1.9 (1.0,3.5)
Presence of radiographic knee OA					
No	844	6759.4	71	10.5 (8.3, 13.3)	1.0 (reference)
Yes	181	1392.6	28	20.1 (13.9, 29.1)	2.2 (0.7,1.9)

* Adjusted for baseline age, sex, BMI, income level, education, levels of occupational physical activity and comorbidities.

radiographic, knee OA, is associated with increased risk of all-cause mortality. Future studies to understand the mechanism linking knee OA and all-cause and cause-specific mortality are warranted.

Author contributions

Conception and design: QL, YZ, JL.
Collection and assembly of data: QL, JH, XT, XW, RL, HL, YK, XZ, KW.
Analysis and interpretation of the data: all co-authors.
Drafting of article: QL.
Critical revision: YZ, JL.
Final approval of the article: all co-authors.
Statistical analysis: QL, JN.
Obtaining of funding: JL, RL.

Conflict of interest

All of the authors have no conflicts of interest to declare.

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Appendix. Association between covariates and all-cause mortality among participants in Wuchuan Osteoarthritis Study

Covariates	Age- and sex- adjusted hazard ratio (95% CI)
Sex (women vs men)	0.7 (0.5, 1.0)*
BMI (kg/m^2)	
Underweight (<18.5 kg/m^2)	1.5 (0.9, 2.5)
Normal weight (18.5–<25 kg/m^2)	1.0 (reference)
Overweight/obesity (≥25 kg/m^2)	0.9 (0.5, 1.9)
Occupational physical activity (severe vs light/moderate)	0.8 (0.5, 1.4)
Education level (middle school or above vs elementary school)	0.9 (0.6, 1.4)
Income (>3000/year vs ≤3000 yuan/year)	0.8 (0.5, 1.3)
Heart diseases (yes vs no)	1.6 (1.0, 2.8)
Hypertension (yes vs no)	1.4 (0.9, 2.4)
Diabetes (yes vs no)	2.0 (0.4, 10.2)
Renal disorders (yes vs no)	2.7 (1.4, 5.5)
Malignant tumor (yes vs no)	4.8 (1.2, 19.8)
Chronic lung diseases (yes vs no)	2.8 (1.7, 4.7)

* Age-adjusted hazard ratio.

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